

Observations on the Modified Wenker Synthesis of Aziridines and the Development of a Biphasic System

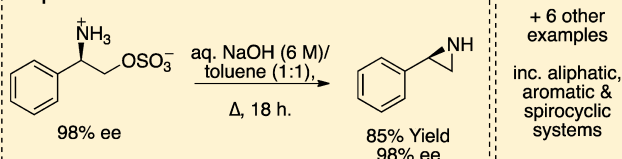
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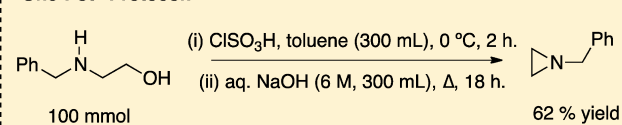
S Supporting Information

ABSTRACT: A cheap and reliable process for the modified Wenker cyclization to afford aziridines has been achieved using biphasic conditions for a range of amino alcohol starting materials. A 100 mmol “one-pot” process has also been devised, and the enantiopurity of the starting amino alcohol is retained in the aziridine product.

Stepwise Protocol:



“One-Pot” Protocol:



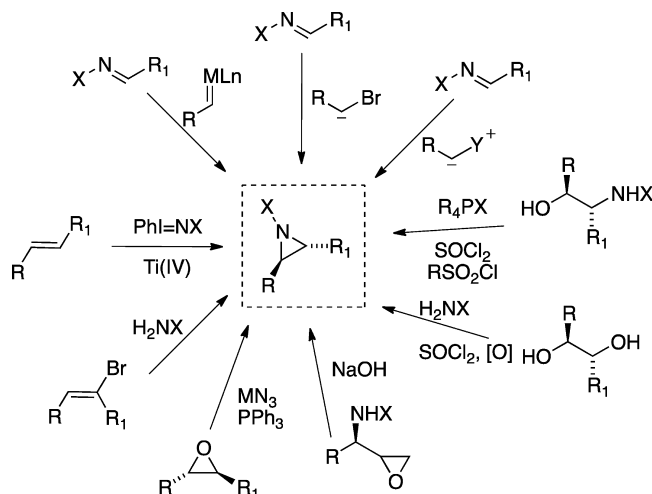
Aziridines are important synthetic building blocks for the construction of complex nitrogen-containing compounds and are found in several natural products, for example the mitomycins and azicemicins. The construction of the aziridine ring system has been studied intensively over many decades, and a host of approaches have been identified, some examples of which are shown in Scheme 1.^{1,2}

Most approaches require the existence of a protecting group at nitrogen, which is invariably a sulfonate group such as the tosyl group. Approaches toward N–H aziridines are much less frequent, and perhaps the most well-known of these is the Wenker synthesis, in which an amino alcohol is first treated with sulfuric acid and then in a subsequent step with base to

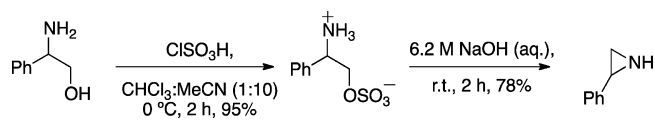
ring close to form the desired aziridine. This is an attractive route due to the plethora of starting materials readily available either through synthesis of amino alcohols or by direct purchase from commercial suppliers. However, the harsh reaction conditions employed in the original synthesis (treatment with sulfuric acid and vacuum dehydration) have precluded its use in some circumstances.

For example, Xu and co-workers have reported some unexpected products that were obtained after treatment of certain amino alcohols under conventional Wenker conditions, in which vicinal amino alcohols in hot sulfuric acid readily undergo elimination of water.^{3,4} In an improved process Xu and co-workers have converted a range of amino alcohols, under mild conditions, into their corresponding hydrogen sulfate salts with chlorosulfonic acid; the sulfates were then cyclized in good yield with sodium hydroxide or sodium carbonate (Scheme 2).⁵

Scheme 1. Common Routes towards Aziridines



Scheme 2. Xu and Co-workers' Route to Aziridines



In connection with a number of research programs in our laboratory we required a mild, reliable, cheap, and scalable synthesis of a range of N–H aziridines. There are a plethora of reports in this area, and we were attracted to the Wenker and related syntheses.^{6–9} Hence we initiated a program to prepare the aziridines required using the mild conditions reported by

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Xu and co-workers above. Synthesis of the hydrogen sulfate adducts 1–6 from amino alcohols was straightforward and proceeded in good to excellent yields, employing chlorosulfonic acid in acetonitrile at 0 °C (Table 1).

Table 1. Synthesis of the Hydrogen Sulfate Adducts^a

Entry	Hydrogen Sulfate adduct	Yield (%) ^b
1		81
2		90
3		70
4		75
5		97
6		73

^aGeneral conditions: Amino alcohol (10 mmol), MeCN (75 mL), 0 °C, chlorosulfonic acid (10 mmol), 3.5 h. ^bIsolated yield.

However, in our hands the synthesis of the cyclized aziridines proved troublesome; for example, when using the hydrogen sulfate adduct 1 the sole product produced when employing aqueous 6.2 M NaOH or saturated aqueous Na₂CO₃ at room temperature was phenylglycinol 7. Increasing the reaction temperature to 70 °C under the 6.2 M NaOH conditions resulted in a 1:1 mixture of phenylglycinol 7 to aziridine 8, which could be further improved, by heating under reflux, to an 84:16 ratio in favor of the aziridine 8. We found that a screen of the NaOH concentration only served to increase the ratio of amino alcohol produced (for example, 12 M afforded a 79:21 ratio in favor of the amino alcohol; see Table 2).

In an attempt to increase the ratio toward an acceptable and reproducible level of aziridine we opted to add a cosolvent to the reaction; a screen shown in Table 3 shows that the use of toluene under biphasic conditions provides the optimal ratio of aziridine product, and an isolated yield of 85% was consistently observed.

Having optimized the conditions for aziridine synthesis from phenyl glycinol hydrogen sulfate we then went on to apply these conditions over a range of substrates for aromatic, aliphatic, and spirocyclic aziridine formation (Table 4). Good to excellent yields were obtained. However, we encountered problems with several substrates due to their volatility; hence we opted to isolate these as the corresponding tosylate, with yields over the two steps varying from 55 to 65%.

In order to test the robustness of the procedure we carried out the cyclization of the phenyl glycinol salt 1 on a larger scale

Table 2. Attempted Synthesis of Aziridines under Aqueous Conditions^a

entry	(aq.) NaOH concn (M)	ratio ^b (amino alcohol 7/aziridine 8)
1	1	68:32
2	2	55:45
3	3	67:33
4	4	52:48
5	5	57:43
6	6	49:51
7	7	57:43
8	8	66:34
9	9	57:43
10	10	59:41
11	11	82:18
12	12	79:21

^aGeneral conditions: 5 mmol of substrate, 6.0 M aq. NaOH/cosolvent (1:1), Δ 18 h. ^bRatio evaluated from the ¹H NMR spectrum by integration of the benzylic C–H peak; isolated yields were typically 60–80%.

Table 3. Cosolvent Optimization for the Synthesis of Aziridines^a

entry	cosolvent	ratio ^b (amino alcohol 7/aziridine 8)	yield ^c
1	none	16:84	nd
2	toluene	5:95	85%
3	EtOAc	<5:<5	nd ^d
4	THF	19:81	nd
5	<i>i</i> -PrOH	50:50	nd
6	MeCN	<5:<5	nd ^d
7	acetone	<5:<5	nd ^d

^aGeneral conditions: 5 mmol of substrate, 6.0 M aq. NaOH/cosolvent (1:1), Δ 18 h. ^bRatio evaluated from the ¹H NMR spectrum by integration of the benzylic C–H peak. ^cIsolated yield after chromatography. ^dComplex mixture observed by ¹H NMR spectroscopy.

(58 mmol); gratifyingly we observed an 80% yield of aziridine. We also carried out the process with enantioenriched starting material and observed complete retention of stereochemical information in the aziridine product (98% ee, Scheme 3).

As the initial sulfate salt was prepared in acetonitrile, filtered, and then resuspended in toluene before addition of the sodium hydroxide, we were intrigued to find out if the process could be converted to a “one pot” protocol. We therefore dissolved 100 mmol of *N*-benzylethanamine in toluene, cooled the solution to 0 °C, and added the chlorosulfonic acid; immediate precipitation of the salt ensued, and after 2 h we directly added sodium hydroxide (6 M) and brought the reaction to reflux. After 18 h the reaction was worked up in the usual manner, and we obtained a 62% yield of the desired aziridine after chromatography (Scheme 4).

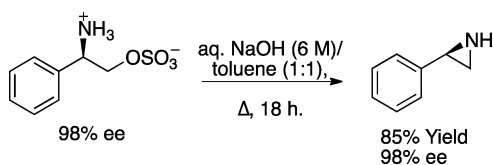
In conclusion we have developed a reliable and cheap approach to simple aziridines under biphasic conditions. We are

Table 4. Aziridine Synthesis^a

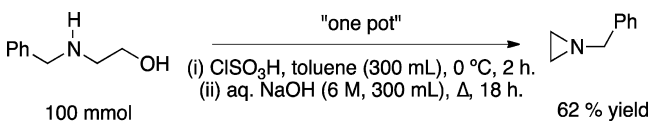
Entry	Hydrogen Sulfate adduct	Aziridine Product	Yield (%) ^b
1	1		85 (82) ^c
2	2		85
3	3		55 ^d
4	4		60
5	5		60 ^d
6	6		65 ^d

^aGeneral conditions: Substrate (5 mmol), 6.0 M aq. NaOH/toluene (1:1), Δ 18 h. ^bIsolated yield after chromatography; yield in parentheses is from a 58 mmol reaction. ^cAverage yield over three individual runs. ^dReaction conditions: (i) Substrate (5 mmol), 6.0 M aq. NaOH/toluene (1:1), Δ 18 h; (ii) *p*-toluenesulfonyl chloride (5 mmol), Et₃N (5 mmol) 12 h.

Scheme 3. Retention of Stereochemical Information after the Cyclization Process



Scheme 4. The "One-Pot" Process



now applying this system to a range of aziridines for use in future research areas.

EXPERIMENTAL SECTION

General Experimental. All infrared thin film spectra were acquired using sodium chloride plates. All ¹H and ¹³C NMR spectra were measured at 400.13 and 100.62 MHz. The solvent used for NMR spectroscopy was CDCl₃ (unless stated otherwise) using TMS (tetramethylsilane) as the internal reference. Chemical shifts are given in parts per million (ppm), and *J* values are given in Hertz (Hz). All mass spectra were recorded by an orbitrap HRMS with an ion max source and ESI probe. Melting points are uncorrected. All chromatographic manipulations used silica gel as the adsorbent. Reactions were monitored using thin layer chromatography (TLC) on aluminum backed plates. TLC was visualized by UV radiation at a wavelength of 254 nm, or stained by exposure to an ethanolic solution of phosphomolybdic acid (acidified with concentrated sulfuric acid), followed by charring where appropriate. Purification by column chromatography used silica adsorbent. Reaction solvents were obtained commercially dry and were used without further purification. The enantiomeric excess was determined by chiral HPLC. A Eurocel 01 (manufactured by Knauer, Chiracel OD equivalent) column was used for the determination of an enantiomeric excess of the nonracemic styrene aziridine reaction on an HPLC instrument, with the ultraviolet absorption detector set at 254 nm, attached to a data station.

Representative Procedure for the Formation of the Aminosulfate Salts. Amino alcohol (10 mmol) was dissolved in acetonitrile (75 mL), and the reaction mixture was cooled to 0 °C followed by the dropwise addition of chlorosulfonic acid (1.17 g, 0.66 mL, 10 mmol). The resulting heterogeneous solution was stirred constantly at room temperature for 3.5 h. The reaction mixture was then filtered under vacuum, followed by washing with ethyl acetate and diethyl ether. The filter cake was dried in air under vacuum and then transferred to an RBF and placed under high vacuum to afford the aminosulfate salt as a colorless solid.

2-Ammonio-2-phenylethyl Sulfate 1.¹⁰ Colorless solid (1.76 g, 81%), mp 245–246 °C (lit.¹⁰ 247 °C); ¹H NMR (400 MHz, CDCl₃) 4.30–4.32 (m, 2H), 4.65–4.69 (m, 1H), 7.38–7.43 (m, 5H) ppm; ¹³C NMR (100 MHz, CDCl₃) 54.0, 68.7, 127.2, 129.3, 129.8, 132.4 ppm; IR (CH₂Cl₂) 998, 1161, 1227, 1252, 1458, 1620, 2943 cm⁻¹; HRMS (ESI) calcd for C₈H₁₁NO₄S (M⁺Na) 240.0306, found 240.0295.

2-Ammonio-3-phenylpropyl Sulfate 2.¹¹ Colorless solid (2.08 g, 90%), mp 266–272 °C (lit.¹¹ 265–270 °C); ¹H NMR (400 MHz, CDCl₃, Me₄Si) 2.90–3.02 (m, 2H), 3.74–3.80 (m, 1H), 3.99 (dd, *J* = 5.9, 11.4 Hz, 1H), 4.16 (dd, *J* = 3.1, 11.4 Hz, 1H), 7.24–7.36 (m, 5H) ppm; ¹³C NMR (100 MHz, CDCl₃, Me₄Si) 33.7, 51.1, 65.6, 126.8, 128.3, 128.6, 134.0 ppm; IR (CH₂Cl₂) 1008, 1170, 1224, 1247, 1457, 1610, 2992 cm⁻¹; HRMS (ESI) calcd for C₉H₁₃NO₄S (M⁺Na) 254.0463, found 254.0451.

2-Ammonio-4-methylpentyl Sulfate 3. Colorless solid (1.38 g, 70%), mp 287–288 °C. Anal. Calcd for C₆H₁₃NO₄S: C, 36.5; H, 7.7; N, 7.1. Found: C, 36.3; H, 7.5; N, 7.0. ¹H NMR (400 MHz, CDCl₃) 0.86 (d, *J* = 6.6 Hz, 6H) 1.42–1.53 (m, 2H), 1.60–1.65 (m, 1H), 3.55–3.61 (m, 1H), 4.02 (d, *J* = 6.6, 11.6 Hz, 1H), 4.20 (d, *J* = 3.2, 11.6 Hz, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃) 21.2, 21.6, 23.7, 37.3, 49.2, 67.4 ppm; IR (CH₂Cl₂) 1004, 1167, 1228, 1259, 1608 cm⁻¹; HRMS (ESI) calcd for C₆H₁₃NO₄S (M⁺Na) 220.0619, found 220.0610.

2-(Benzylammonio)ethyl Sulfate 4.¹² Colorless solid (1.73 g, 75%), mp 245–247 °C (lit.¹² 244–246 °C); ¹H NMR (400 MHz, CDCl₃) 3.36–3.38 (m, 2H), 4.25–4.28 (m, 4H), 7.44 (s, 5H) ppm; ¹³C NMR (100 MHz, CDCl₃) 45.9, 51.0, 63.4, 129.3, 129.7, 129.9, 130.4 ppm; IR (CH₂Cl₂) 1028, 1192, 1214, 1251, 1457, 1613, 3003 cm⁻¹; HRMS (ESI) calcd for C₉H₁₃NO₄S (M⁺Na) 254.0463, found 254.0449.

2-Ammonio-3,3-dimethylbutyl Sulfate 5. Colorless solid (1.68 g, 97%), mp 278–280 °C. Anal. Calcd for C₆H₁₃NO₄S: C, 36.5; H, 7.7; N, 7.1. Found: C, 36.6; H, 7.5; N, 6.9. ¹H NMR (400 MHz, CDCl₃) 0.98 (s, 9H), 3.31 (dd, *J* = 3.3, 8.8 Hz, 1H), 4.08 (dd, *J* = 8.8, 11.4 Hz, 1H), 4.30 (dd, *J* = 3.3, 11.4, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃) 25.3, 31.7, 59.3, 65.8 ppm; IR (CH₂Cl₂) 1009, 1180, 1219, 1246, 1611

cm⁻¹; HRMS (ESI) calcd for C₆H₁₅NO₄S (M⁺Na) 220.0619, found 220.0609.

(1-Ammoniocyclopentyl)methyl Sulfate **6**. Colorless solid (1.42 g, 73%), mp 258–260 °C. Anal. Calcd for C₆H₁₃NO₄S: C, 36.9; H, 6.7; N, 7.2. Found: C, 36.8; H, 6.7; N, 7.1. ¹H NMR (400 MHz, CDCl₃) 1.67–1.79 (m, 6H), 1.86–1.93 (m, 2H), 4.04 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) 23.8, 33.4, 63.3, 70.6; IR (CH₂Cl₂) 999, 1108, 1207, 1246, 1634 cm⁻¹; HRMS (ESI) calcd for C₆H₁₃NO₄S (M⁺Na) 218.0463, found 218.0451.

General Procedure for the Cyclization To Form Aziridines. N-H Aziridines. Aminosulfate salt (5.0 mmol) was dissolved in NaOH (40 mL, aq. 6 M) followed by the addition of toluene (40 mL). The resulting biphasic solution was heated under reflux for 18 h with constant stirring. On completion the organic phase was extracted with ethyl acetate, dried over MgSO₄, and evaporated under reduced pressure, followed by purification by column chromatography on silica gel, affording the aziridine as a colorless oil.

N-Ts Aziridines. Aminosulfate salt (5.0 mmol) was dissolved in NaOH (40 mL, aq. 6 M) followed by the addition of toluene (40 mL). The resulting biphasic solution was heated under reflux for 18 h with constant stirring. On completion the organic phase was extracted with ethyl acetate, dried over MgSO₄, and evaporated under reduced pressure, followed by addition of *p*-toluenesulfonyl chloride (0.95 g, 5.0 mmol) and triethylamine (0.51 g/0.70 mL, 5.0 mmol). The resulting reaction mixture was stirred at room temperature for 12 h. On completion the reaction mixture was washed with water, extracted, dried over MgSO₄, and evaporated under reduced pressure followed by purification by column chromatography on silica, affording the aziridine as a colorless solid or oil.

2-Phenylaziridine 8.¹³ Colorless oil (0.51 g, 80%); ¹H NMR (400 MHz, CDCl₃) 1.83 (d, *J* = 3.2 Hz, 1H), 2.24 (d, *J* = 6.0 Hz, 1H), 3.04–3.06 (m, 1H), 7.25–7.36 (m, 5H) ppm; ¹³C NMR (100 MHz, CDCl₃) 29.3, 32.1, 125.7, 127.1, 128.5, 140.5 ppm; HRMS (ESI) calcd For C₈H₉N (M⁺H) 120.0808, found 120.0807.

2-Benzylaziridine 9.¹⁴ Colorless oil (0.57 g, 85%); ¹H NMR (400 MHz, CDCl₃) 1.46 (d, *J* = 3.6 Hz, 1H), 1.83 (d, *J* = 4.7 Hz, 1H), 2.19–2.25 (m, 1H), 2.66 (dd, *J* = 6.0, 14.6 Hz, 1H), 2.81 (dd, *J* = 6.0, 14.6 Hz, 1H), 7.21–7.33 (m, 5H) ppm; ¹³C NMR (100 MHz, CDCl₃) 24.8, 31.00, 40.0, 126.4, 128.5, 128.8, 139.2 ppm; HRMS (ESI) calcd For C₉H₁₁N (M⁺H) 134.0970, found 134.0980.

2-iso-Butyl-1-tosylaziridine 10.¹⁵ Colorless oil (0.76 g, 60%); ¹H NMR (400 MHz, CDCl₃) 0.88 (dd, *J* = 2.1, 4.7 Hz, 6H), 1.28–1.40 (m, 2H), 1.57–1.6 (m, 1H), 2.02 (d, *J* = 4.7 Hz, 1H), 2.45 (s, 3H), 2.63 (d, *J* = 7.1 Hz, 1H), 2.76–2.82 (m, 1H), 7.34 (d, *J* = 8.5 Hz, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃) 21.7, 21.9, 22.8, 26.8, 34.1, 39.1, 40.4, 128.0, 129.6, 135.3, 144.4 ppm; IR (CH₂Cl₂) 2958, 1494, 1376, 1365, 1184 cm⁻¹; HRMS (ESI) calcd. For C₁₃H₁₉NO₂S (M⁺Na) 276.1034, found 276.1021.

1-Benzylaziridine 11.¹⁶ Colorless oil (0.40 g, 60%); ¹H NMR (400 MHz, CDCl₃) 1.28 (t, *J* = 2.4 Hz, 2H), 1.83 (t, *J* = 2.4 Hz, 2H), 3.39 (s, 2H), 7.24–7.37 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) 27.6, 65.3, 127.0, 128.0, 128.4, 139.3 ppm; IR (CH₂Cl₂) 1358, 1496, 3031 cm⁻¹; HRMS (ESI) calcd for C₉H₁₁N (M⁺H) 134.0970, found 134.0963.

2-tert-Butyl-1-tosylaziridine 12.¹⁷ Colorless solid (0.82 g, 65%), mp 58–60 °C (lit.¹⁷ 58.5–59.2 °C); ¹H NMR (400 MHz, CDCl₃) 0.79 (s, 9H), 2.17 (d, *J* = 4.5 Hz, 1H), 2.44 (s, 3H), 2.49–2.57 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃) 21.6, 26.2, 30.1, 30.3, 48.9, 128.2, 129.6, 135.2, 144.4 ppm; IR (CH₂Cl₂) 2958, 1598, 1368, 1322, 1185 cm⁻¹; HRMS (ESI) calcd for C₁₃H₁₉NO₂S (M⁺Na) 276.1034, found 276.1020.

2-Cyclopentyl-1-tosylaziridine 13. Colorless solid (0.82 g, 65%), mp 77–79 °C (lit. 82–83 °C); ¹H NMR (400 MHz, CDCl₃) 1.66–1.91 (m, 6H), 2.17–2.27 (m, 2H), 2.43 (s, 3H), 2.55 (s, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.83 (d, *J* = 8.3 Hz, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃) 21.6, 25.6, 32.3, 40.7, 56.7, 127.5, 129.5, 137.5, 143.9 ppm; IR (CH₂Cl₂) 2960, 1599, 1364, 1319, 1184 cm⁻¹; HRMS (ESI) calcd for C₁₃H₁₇NO₂S (M⁺Na) 274.0878, found 274.0866.

The One-Pot Protocol. *N*-Benzylethanolamine (15.2 g, 100 mmol) was dissolved in toluene (300 mL), and the reaction mixture was cooled to 0 °C followed by the dropwise addition of chlorosulfonic

acid (11.7 g, 6.6 mL, 100 mmol). The resulting heterogeneous solution was stirred constantly at room temperature for 2 h. NaOH (300 mL, aq. 6 M) was added, and the resulting biphasic solution was heated under reflux for 18 h with constant stirring. On completion the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The organics were combined, dried over MgSO₄, and evaporated under reduced pressure to afford a pale yellow oil. Purification by column chromatography on silica gel afforded the aziridine **11** as a colorless oil (8.25 g, 62%).

■ ASSOCIATED CONTENT

📄 Supporting Information

Copies of all ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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